REMARKS

Applicants submit this response to the Office Action dated December 2, 2003. Claims 1-3 and 6-15 were previously cancelled, and claims 5, 16-41 and 47-48 are withdrawn. Claims 4, 42, 43 and 44 have been amended as discussed below, and no new matter is added.

In the Office Action, claims 4 and 42-46 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse on the grounds that by disclosing a sequence for the polypeptide of huBUB3, and the functional characteristics of huBUB3, applicants have disclosed the features of the genus of huBUB3 polypeptides. The application therefore provides description of the huBUB3 polypeptides as claimed in claims 4 and 42-46, as amended.

In support of the rejection, the Examiner has cited case law that allegedly supports the premise that the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, and that the specification fails to define any variant or epitope-bearing portion of huBUB3 protein. Applicants submit that none of the case law cited by the Examiner is on point, as discussed below.

The Shokal decision, 113 U.S.P.Q. 283 (C.C.P.A. 1957) is a case in the chemistry arts. The Court discussed an earlier decision, Joseph V. Meigs v. James McIntosh, 17 C.C.P.A. 852 (1930), in which disclosure of carbohydrates in general, use of a specific example, and a claim to water soluble carbohydrates, was based upon the specific disclosure thereunder consideration. (113 U.S.P.Q. at 286). Thus, the Court indicated that each case is fact-specific, and the Shokal case fails to support a finding that the present applicant's disclosure does not support a genus. At issue in Shokal was the written description for the second component of a compound, which was described as a "neutral compound free of elements other than carbon, hydrogen and oxygen." (113 U.S.P.Q. at 285). The Examiner in the Shokal case stated that the claims read on literally thousands of known comonomers (113 U.S.P.Q. at 285).

The Shokal Court stated that the disclosure can point out a genus by statements of principles and specific examples (113 U.S.P.Q. at 285). In the present application, such a statement of principle is met by the disclosure of a human BUB3 protein, which for the purposes of analysis herein can be considered a genus. The specific examples that support the scope of the claims are BUB3 proteins with one or more conservative amino acid substitution and variants of

BUB3 protein. Support for such substitutions is found in the specification as filed at page 9, lines 1-16, and variants are supported at page 9, lines 25-31.

The Examiner also cited Purdue Pharma, 56 U.S.P.Q.2d 1481 (C.A.F.C. 2000), to support his position that the disclosure of a single species may not support a broad genus, particularly when the specification fails to describe the features of that genus even in passing. In the present case, one cannot say that the specification fails to describe the features of that genus "even in passing," because the specification clearly discloses and describes huBUB3 protein and variants thereof. Furthermore, the Purdue case is not on point because it involves pharmaceutical compositions, and whether the specification conveys a specific plasma concentration after administration of a particular dosage form. The written description in the Purdue case cannot be readily applied to a situation in which an amino acid sequence is provided and directions are given in the specification for substituting one or more conservative amino acids. Purdue is fact specific and relates to dosage ranges, not a composition.

The Pfaff decision, 48 U.S.P.Q.2d 1641 (1998), also is not on point. This case relates to an on-sale bar, not to written description, and Section 112 was not applied at all in the decision. The issue raised was whether the product, a computer chip socket, was ready for patenting. The Court determined that the invention was ready for patenting because drawings that the inventor sent to the purchaser fully disclosed the invention.

The next case cited by the Examiner, Eli Lilly, 43 U.S.P.Q.2d 1406 (1991), also is not on point. The patent application disclosed a rat sequence for insulin, and contained one constructive example on how to obtain human sequence, but provided no disclosure of which amino acids to substitute, add or delete from the rat sequence to obtain the human sequence. In contrast, the present invention does teach the substitution of one or more conservative amino acids in a disclosed sequence. The Court in Lilly stated, "Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." (43 U.S.P.Q. 2d at 1568.) That statement is not applicable to the present situation, where the material, human BUB3 protein, is specifically known to exist, and so a situation involving the absence of knowledge as to what that material consists of simply is not applicable to the present invention. The Lilly case presented a situation in which the applicants claimed a nucleotide sequence from one species, wherein they disclosed a polynucleotide sequence from a different species, and the application did not suggest specific amino acid

substitutions, additions or deletions in order to derive the second polynucleotide sequence from the first. The Court specifically declined to apply this reasoning to a situation such as the present one. "We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the 525 patent's written description supported only by the specific nucleotide sequence of rat insulin." (43 U.S.P.Q. at 1569.) Thus, the Lilly case does not support a position that disclosure of a sequence of a specific protein fails to provide written description for variants of that same protein.

The Amgen case cited by the Examiner, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), also is not on point. The Amgen case relates to reduction to practice for purposes of priority of invention, not to written description. The Court held that the inventor would have to clone the sequence in order to obtain the sequence information, as the amino acid sequence was unknown. The holding of the case relates to conception, not written description, and to best mode. However, if the reasoning were applied to the present case, applicants' specification does not present a situation where the amino acid sequence is unknown; on the contrary, the amino acid sequence is known, and also known are possible conservative amino acid sequence substitutions that can be performed to obtain other members of this genus.

The Examiner also asserted that the state of the art at the time of filing was such that defining epitopes was not "as easy as it seems" (Office Action, page 5, line 11). In support, the Examiner cited Greenspan et al., Nature Biotechnology 7:936-937, 1999. The Greenspan article relates to defining epitopes, not to determining an epitope for a particular protein. The resolution therefore is to indicate which definition is used in the document in question. In the last sentence of Lies article, Greenspan states: "The result is a confusing divergence between the textbook definition of epitope and the definition that is often actually in use, in published descriptions of experimental investigations." In patent practice, there can be a divergence between the definition of a term in a patent application and a meaning that someone else may give to the term. To remedy this, the doctrine is applied wherein the patentee is his or her own lexicographer. If the patent application does not define a term that one of skill in the art would be familiar with, then one relies on the most usual definition. Epitopes are described in the present application at page 14, lines 3–19. As the application does not provide a definition for epitope that is intended to differ from the way the term is used in the art, then applicant can rely

on the definition of epitope as it was known in the art at the time of filing. Regarding the Ngo reference (in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston, Boston, MA, 1994), this reference relates to the theoretical issues of protein folding. One of skill would be aware of such issues and they are included into the appropriate factors for determining "undue experimentation." Nothing in Ngo contradicts the premise that one of skill is prepared, under Wands and Forman, to conduct experimentation in the antibody art. Similar arguments apply to Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, 1976). What Rudinger referred to as "painstaking" experimental study (page 6) in 1976 was at the time of filing, in 1997-1998, far more routine, and, again, one of skill in the antibody art is aware of the potential need for such experimentation. In fact, known methods for producing peptides, analogs and derivatives are cited in the specification, for example at page 10, lines. 26-30.

For the foregoing reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph (written description) is respectfully requested.

Claims 4 and 42-46 are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly is not enabling for any variant or epitope-bearing portion of SEQ ID NO:2. Applicants respectively submit that the claims as amended are enabled under the standards set forth in Wands as provided by the Examiner.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may

be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q.2d at 1407. Thus, Wands supports the conclusion that in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma capable of making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate a finding that the amount of experimentation to achieve a positive result is undue.

Like the production of monoclonal antibodies, the identification or production of a huBUB3 polypeptide falling within the scope of the present claims may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain a polypeptide that is within the scope of the claims.

Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* To obtain a polypeptide within the scope of the claims, the only experimentation required is the performance of known genetic engineering procedures. These procedures are routine and would not have to be done repeatedly before a definitive result was obtained. Because the inventors and the art provide means for the objective measurement of a polypeptide falling within the claim scope, this factor is met, for

example, by the ability to modify the amino acid sequence and determine if the resulting protein retains 95% identity to SEQ ID NO:2, or is encoded by a polynucleotide having 90% identity to SEQ ID NO:1.

The Wands court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (U.S.P.Q.2d at 1406.) The court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (U.S.P.Q.2d at 1406).

By analogy, a single experiment in the present art could include obtaining or constructing a polypeptide, determining the amino acid sequence of the polypeptide, and comparing it with SEQ ID NO:2. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation, and cites to published scientific articles for details not mentioned in the specification. Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent application at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8 U.S.P.Q.2d at 1404, 1405). The antibody used in applicants' methods is raised using materials based on a commercial plasmid, and the application describes the methods at pages 64-66.

3. *Presence or absence of working examples.* As a working example, the specification describes production of protein using a polynucleotide of the invention, specifically huBUB plasmid 291-2. (Page 53, lines 6-11.)

4. *Nature of the invention.* The invention relates to human polypeptides. Methods of synthesizing, isolating, mutating, manipulating, transfecting, and expressing polypeptides are the basis for the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in Wands stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in

that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation (8 U.S.P.Q.2d at 1406-1407).

5. *The state of the prior art.* The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of polypeptides, specifically huBUB3 polypeptides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 U.S.P.Q.2d at 1406). Similarly, the methods of constructing or expressing protein and determining amino acid sequences are well known.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 U.S.P.Q.2d at 1406). By analogy, it would not defeat enablement for one of skill in the art of protein chemistry and sequencing to learn and become proficient in techniques for practicing the present invention.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when routine procedures are used to modify the codons corresponding to conservative amino acid changes in SEQ ID NO:2, polypeptides can be expressed that will have an amino acid sequence falling within the scope of the claims, and this can be routinely confirmed by amino acid sequence determination and alignment with SEQ ID NO:2.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the polypeptide expression, construction, and sequencing steps would be "more difficult or unreliable" (8 U.S.P.Q.2d at 1406) than for SEQ ID NO:2.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any polypeptide molecule meeting

the limitations of the claims, and test it for percent identity to SEQ ID NO:2 as described for the previous factors.

In view of the foregoing remarks, applicants submit that the Examiner has not met his burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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